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(54) Chip construction with DNA technology.

(57) The invertion relates to construction of specific molecular microcircuits by the use of double and single stranded nucleic acids and specific DNA-binding proteins.

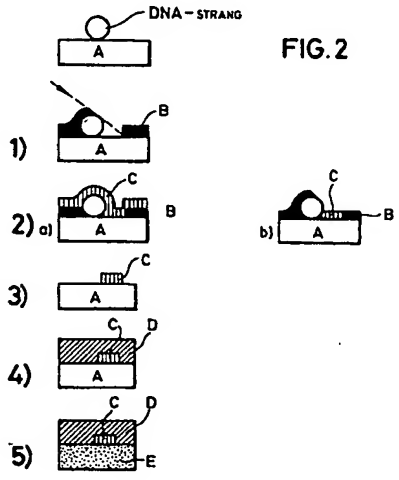

FIG. 2

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DNA is a polymeric compound which can be manipulated by different physical and enzyme techniques such as denaturation/renaturation, enzymatic synthesis, modification reactions and protein binding. DNA technology (ref.8) allows the construction of self assembling networks at a ultramicroscopical or monomolecular scale (described below). The nucleic acid networks can be used as masks in photolythographic procedures currently used for the construc tion and production of computer chips. The networks can be reproduced by moulding to produce replicas consisting of other materials or can be used as a scaffold to deposit different materials such as n- doped gallium arsenide or gallium arsenide, able to conduct electric current. So constructed conducting elements can be used as components of electronic chips. The self assembling properties of nucleic acids can be also used to construct switching elements needed for electronic chips.

We describe a methodology that allows the construction of molecular micro-circuits using recombinant DNA technology and related biochemical techniques.

The advantages of this methodology are:

Miniaturization. The networks form as a consequence of programmed reactions which are determined by the structure of the components of the network e.g. the base sequence of the nucleic acids. Therefore, their design and production do not depend upon photolythographic reproduction of a large-scale predesigned network. Thus, the size and precision limits intrinsic to commonly used reproduction procedures are a priori by-passed by our method. The size of the circuits is close to that of the thickness of a single or double-stranded nucleic acid (from 10 to 20 Å) and far below the sizes obtainable at present.

Precision. This is determined by the high precision possible for the reactions of nucleic acid biosynthesis: an average of one error per 10^9 nucleotides incorporated into a polymeric chain. Furthermore the high specificity of base pairing ensures a high precision of the assembly of the network components. Thus, both the miniaturization and accuracy of the microcircuits obtainable by our DNA chip technology are at least two orders of magnitude higher than that of the normal photolythographic procedure.

We describe, in the following order, the principles (and relevant examples) underlying the construction of micropatterns and their use as electronic chips.

I Construction of nucleic acids networks

II The conversion of nucleic acid or nucleic acid-protein networks to an electricity-conducting network.

III The nucleic acid or nucleic acid-protein networks described in I and II can also be used for a: Photolithographic reproduction method using the DNA network as a mask.

I CONSTRUCTION OF NUCLEIC ACIDS NETWORKS

1. Construction of initiation point (DWIP) and end point (DWEP) of the DNA wire.

A network made up of nucleic adds consists of a DNA wire initiation point (sect.1a), of an intermediate part (sect.1b, 1c and 2-4), of a DNA wire end point (sect.1c). The complexity of the intermediate part can be programmed and can consist of branch points, switches and multistranded DNA regions (sect.2).

a. DNA wire initiation point.

A DWIP, DNA wire initiation point, is constructed by use of a DNA doubler strand having a blunt end at one extremity and a sequence specific single stranded extension at the other end such that only one end is a substrate for DNA elongation by synthesis or hybridization.

Outline 1

An oligonucleotide with the following sequence can be synthesized *in vitro*:

3'TTAACTGAACTAGAGAACGTCTAGTTCAGTTAACT-

-ATTTTGGAAGCGTAGCTTCCACTAATCCT5' (1)

3' and 5' indicate the 2 extremities of the nucleic acid strand. The enzymatic polymerization of DNA by the enzyme DNA polymerase (ref.7) proceeds by addition of monomers to the 3'-extremity (see ref.1). The letters G,A,C,T are acronyms that indicate the monomeric constituents of the DNA strand; they are nucleotide monophosphates containing respectively a purine (guanine for G, adenine for A) or a pyrimidine

(cytosine for C, thymine for T) residue. In DNA polymers these compounds can base pair specifically: G couples always with C, A with T. Therefore a self-annealing reaction in a solution containing the appropriate buffer (2x SSC solution, ref.8 p.447) at 20°C will produce the molecule.

```
   ,AG AGATCAAGTCAATT3'
A   ||||||||||||||||
   `CGTCTAGTTCAGTTAACTATTTTGGAAGCGTAGCTTCC-
```

(2)

```
-ACTAATCCT5'
```

The left extremity of molecule (2) is the DWIP, the right extremity is the growing point (that is the point onto which additional hybridization or synthetic reactions can be performed in order to elongate the chain and/or create branch points or switches. Elongation may be obtained by hybridization of a preformed DNA molecule or a reaction of DNA synthesis. Hybridization of nucleic acids is a procedure that exploits the tendency of nucleic acids to anneal to double strand structures (according to the rules mentioned above: A with T, G with C), if the complementary order of the nucleotides that compose the DNA sequence permits it.

One synthesizes according to the procedure mentioned above the following molecule:

GATAAAACCTTCCATAACAAAGTGGTTGAA (3)

The hybridization reaction between molecules (2) + (3) will produce molecule (4):

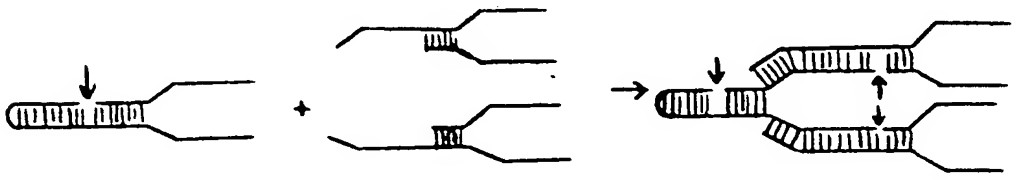
```
   ,AG AGATCAAGTCAATTGATAAAACCTTC-
A   |                          /
   `CGTCTAGTTCAGTTAACTATTTTGGAAG-
```

(4)

```
-CAT AACAAAGTGGTTGAA
   | | |
-GTA GCTTCCACTAATCCT
```

This molecule produced by synthesis and hybridization has one DWIP (left) (defined above as "blunt end") and a branched extremity (right). This branched extremity now provides two different growing points that can be used for further elongation and branching of the molecule, to produce a network (Scheme 1)). Many DNA sequences can lead to the shown below structure. The length is variable.

Scheme 1:



Single strand interruptions in the DNA strands (indicated in Scheme 1 by the arrows), can be easily filled up by the reaction of the enzyme DNA ligase (commercially available, i.e. from Bethesda Research Laboratories, Boehringer Mannheim, etc., see refs. 8,9). The synthesis of oligonucleotides (molecules 1 and 3) can be performed with commercially available apparatus (i.e. from Applied Biosystems or New Brunswick Scientific Company).

The DWIP can be fixed to a solid matrix by several techniques e.g. locally fixed charged molecules or sequence specific DNA binding proteins (as bacteriophage DNA binding proteins, Adenovirus binding protein, lac repressor or synthetic DNA binding proteins) or covalent chemical binding.

Outline 2

A DNA molecule such as molecule (4) described in outline 1 can be fixed by the following procedure to a matrix onto which the nucleic acid network will be formed:

(i) Place, by the use of a micromanipolator, a microdrop of a solution of a specific protein (i.e. lambda-protein repressor; see below) on a hydrophobic surface like polyethylen and let it dry.

(ii) Synthesize a molecule (5) which contains the sequence (4) and (6) in such an arrangement that sequence 6 is located at the left end of the self-annealed double stand structure:

```
    AG TACCTCTGGCGGTGATAAGATCAAGTCAATTGAT-
A                                        /
 CG ATGGAGACCGCCACTATTCTAGTTCAGTTAACTA-
```

Sequence 6 (plus GAACG) Sequence 4 (without GAACG)

(5)

```
-AAAACCTTCCAT AACAAAGTGGTTGAA
 |          |
-TTTTGGAAGGTA GCTTCCACTAATCCT
```

(iii)Treat the hydrophobic surface with a solution of DNA molecule (5). The specific binding of the DNA molecule to the protein molecule is ensured by the use of the specific DNA-protein interaction. Specificity of such interaction is a well-known phenomenon in biological processes and several DNA-protein interaction systems can be chosen, as detailed in the following paragraph.

Repressors are proteins which regulate gene expression, well described for bacteria and bacteriophages systems (ref.11). These proteins interact with DNA with extreme, sequence-determined specificity. A sequence 12-20 nucleotides long is sufficient to determine an absolutely selective DNA-protein interaction. For instance: lambda repressor binds to the DNA sequence:

```
TACCTCTGGCGGTGATA
|               \
ATGGAGACCGCCACTAT
```

(6)

lac repressor binds to the DNA sequence:

```
TGGAATTGTGAGCGGATAACAATT
|                       /
ACCTTAACACTCGCCTATTGTTAA
```

(7)

(iv) Thus the λ-repressor molecule fixed to the polyethylene surface will bind a specifical DNA molecule (5) with high affinity and stability (binding constant of the order of $K_m = 10^{-13}$ M).

(v) An alternative procedure for sequence-specific fixation of polymeric DNA molecule is based on the properties of specific interaction of homogeneous repetitive polynucleotides, such as

GAAGAAGAA... or ... TTTTTTTT... or ... GCGCGCGC... (8)

with oligopeptides made of repetitions of amino acids, such as polylysine, polythreonine, etc.

Specific interaction of oligonucleotides and oligopeptides is common knowledge.

As described above, the DNA in the DWIP can consist of complementary strands which bind specifically to the appropriate protein (see above).

b. Extension of the DWIP.

The right extremity of the DNA molecule (5) is bifurcated and offers two growing points, which can be elongated by hybridisation of a presynthesized or naturally specific DNA strand of a given length and/or by DNA synthesis.

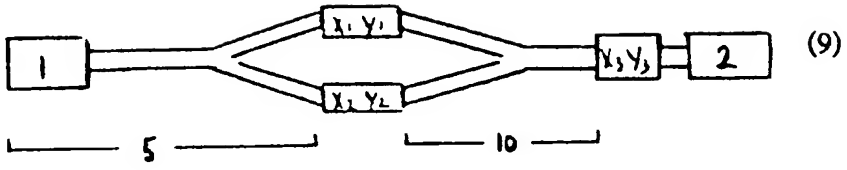
c. DNA wire end point (DWEP).

Construction of a connection between two fixed points.

The DWEP is constructed in a fashion similar to the DWIP. The extension reactions as described for the DWIP can also be applied to the DWEP leading to a connection in between the DWIP & DWEP. The connection can be obtained by hybridization of sequence-specific nucleic acid strands. Alternatively, the extension of the DWIP can be designed to be connected directly to the DWEP by specific hybridization

of a defined DNA strand.

Example 1



(9)

In the above scheme (9) molecule (5) serves as DWIP: Block 1 symbolizes the DNA sequence that binds specifically the lambda repressor;block 2 symbolizes the specific lac repressor binding sequence, the symbols X1Y1, X2Y2, X3Y3 indicate any sequence of any length or any composition, chosen according to the complexity requirement of the micropattern (see below). These intermediate sequences can he easily synthesized *in vitro* with state of art DNA technology or can be prepared from DNA of biological origin (see below). Sequence 10 is built up as sequence (5) but with an other DNA sequence.

In order to obtain a fixed DNA pattern, the following operations are required:

1)Synthesize a DWIP (i.e., molecule (5))

2)Bind it to a fixed lambda repressor molecule, as described

3)Synthesize a DWEP, as described e.g. at the right extremity of molecule (9)

4)Bind it to a fixed lac repressor molecule, as described for the lambda repressor

5)The required intermediate series of DNA molecules above indicated as X1Y1 and X2Y2 are annealed by standard DNA-DNA hybridization procedures to both the DWIP and DWEP. DWIP and DWEP will be located, on a hydrophobic surface, at a distance corresponding to the length of the intermediate part (i.e., for an intermediate of a linear length of 3000 nucleotides, the DWIP and DWEP are 1 µ apart).

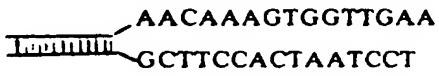
2.Construction of branch points, switches and multistranded regions to be used in DNA wires.

The programming of synthesis of defined DNA sequences, joining them by sequence specific hybridization and - if wanted - the sealing of the single stranded interruptions in the double strands so obtained, offers the possibility of constructing at will any shape of network.

Example 2

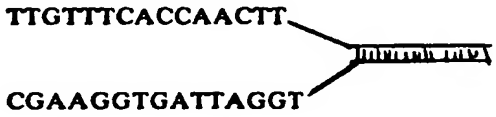
The following constructions are performed

1) a double stranded DNA molecule (10) ending with two protruding single strand sequences



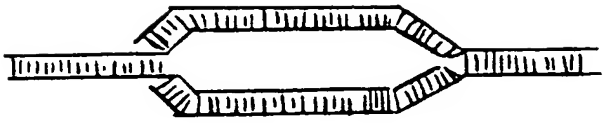
(10)

2) a double stranded molecule (11) ending with two protruding single strand sequences complementary to those of (10):



(11)

3) Molecules 10 and 11 are annealed which leads to a double stranded loop (12)



(12)

Both molecules (10) and (11) can be fixed to a matrix as described for DWIP and DWEP. The length and sequence of each branch can be varied at will. The resulting electronic properties (see below) can therefore be fixed in a preprogrammed fashion. One or both branches can contain specific binding sites for proteins. The binding of the protein allows a change in the electronic properties of the resulting network. Protein-DNA binding systems can be used which only bind under certain electronic conditions in the DNA strands thereby enabling the function of a switching element.

3.Defined DNA length or amount.

DNA is available in defined amounts, sizes, and composition e.g. in the form of plasmids, viral genomes or synthetic DNA. These units can be used for the construction of DNA elements requiring a defined amount of DNA of a defined composition. A unit bound at a specific point determined by the DNA sequence can give desired properties as e.g. a contact point.

4.DNA-protein complexes.

Specific combinations of DNA sequences and DNA binding proteins can be used to construct functional parts in a network. e.g.: A pox virus genome has a protein bound specifically at its extremity (ref.1). This protein can be used to bind the terminal DNA fragment at a matrix. Furthermore many regulatory proteins with specific binding properties such as lac-repressor, λ-repressor etc. are known. Alternatively, polypeptides can be synthesized to bind at specific DNA sequences. In addition modified nucleotides reacting with specific antibodies can be positioned at the end of a DNA molecule i.e., DNA sequences that form left-handed DNA and react with specific antibodies (ref.2).

Specific polypeptide - DNA complexes can be used to fix DNA fragments e.g. to a matrix or to other DNA molecules. In addition or alternatively, antibodies can be used to stick DNA- protein complexes to other compounds or surfaces DNA- protein complexes can also be used to change local electric conductance properties.

5. Use of RNA.

Sequence-specific RNA can be synthesized in vitro on programmed DNA templates (ref.3). The properties of RNA differ from those of DNA. Additionally, RNA can assume, by intrastrand hybridization, any designed secondary structure, such as hairpin-like structures (ref.4), thus offering additional possibilities of modulation of electric conductivity. Mixed RNA-DNA networks can be easily obtained by programming the order of the hybridization (or synthesis) reactions used to construct the connections between DWIP and DWEP.

6. Further examples

Example 3

Simplified protocol for the physical orientation of a DNA double strand to be used as a mould, scaffold or a mask for construc tion of chips:

Step 1: Construct a DWIP with a micromanipulator on a hydrophobic surface such as polyethylene by using a micro- drop of a λ-repressor solution and letting it dry.

Step 2: Construct a DWEP as in step 1, 50 micrometer apart from the DWIP, using an E. coli lac-repressor solution.

Step 3: Prepare a plasmid DNA molecule (ref.8) carrying both the lac operator and the λ-operator.

Since both operators can be integrated at any desired distance within a plasmid, DNA molecules of the desired length carrying terminal operators can be produced by using standard recombinant DNA techniques. Using bacteriophage T4 DNA the size of the bridge molecule could can be as long as 165 kb, whereas a small artificial plasmid that can be amplified in E. coli could be as short as 1 kb. Larger molecules can also be replicated and prepared in the yeast Saccharomyces cerevisiae as minichromosomes (ref.13).

Step 4: Treat the hydrophobic surface with a solution containing this DNA. One DNA molecule will bind selectively and directionally to DWIP and DWEP.

Example 4

Construction of shorter bridges can use cosmid vectors. Short description: restrict cosmid vector DNA. Ligate with DNA of about 49 kb (approx. 15 <m) which contains at one extremity a lac operator and at the other end a λ-operator. The construction is obtained by standard genetic engineering procedures (ref.8): Packaging the ligated DNA *in vitro*, transformation of E. coli, normal selection and ampli fication procedures (ref.8). Use this DNA in the scheme described for example 3, starting from step 3. Distance from DWIP and DWEP = 15 micrometer.

Example 5

Larger bridges between DWIP and DWEP may be constructed by using E. coli chromosomal DNA with specifically inserted lysogenic phage DNA or by recombination inserted DNA segments. Larger defined DNA segments can also be constructed and produced in the yeast Saccharomyces cerevisiae by the use of plasmids (ref.12) or artificial chromosomes (ref.13). Such DNA molecules carry both λ-operator and lac operator DNA sequences, spaced by any desired distance within the DNA element used. Therefore, these DNA molecules can bridge a broad spectrum of distance between DWIP and DWEP, from few nucleotides to more than 1 mm (the length of the linearized E. coli chromosome) or more mm (the length of a yeast chromosome). Use the constructed DNA molecules as described in example 3, starting from step 3.

II CONVERSION OF A NUCLEIC ACID OR NUCLEIC ACID-PROTEIN NETWORK TO AN ELECTRONIC MICROCIRCUIT

The DNA networks can be used as moulds or scaffolds to produce replicas consisting of other materials. The replicas can be made as MOSFETS (metal oxide semiconductor field effect transistors), MESFETS (metal semiconductor FETS), and MODFETS (modulation FETS) by depositing in various orders different materials in selected sequences:

A) Use of shadowing technique to deposit the conductor. The building principle (see Fig. 1) is based on the construction of a molecular nucleic acid network (as described in I) on a support of substrate A of defined chemical characteristics allowing to perform the following steps:

1) Shadow (low-angle) the network with substance B using technic currently practised for the preparation of DNA for EM (ref 5,6) but without rotation leading to an uncovered track along the nucleic acid (Fig.1,1). The substrate is titled by a small value angle relative to the gas flow direction in order to obtain an empty shadow which follows the track defined by the DNA (refs.5,6).

2)

a. Deposit a layer of substance C e.g. doped gallium arsenide, doped silicium, or a similar conductor on the support on which the network is laid and the substance B has been deposited, by metallo-organic chemical vapor deposition (MOCVD). MOCVD, that is by the normal metallo-organic deposition technique already in use in the electronics industry to prepare binary semiconductors (Fig.1, 2).

b. Alternatively substance C can be deposited by electrical deposition only at the track along the nucleic acid pattern.

3) Remove substance B and DNA leaving the conductor pattern free.

4) Deposit a second conductor D e.g. gallium arsenide.

5) If desired remove substance A and replace by another support, substance E.

This procedure leads to the substitution of a molecular nucleic acid/protein pattern by the conductor C embedded in the conductor D.

B) Alternatively, electric deposition of the conductor C directly onto the nucleic add network. Continue with step 5.

III PHOTOLITHOGRAPHIC REPRODUCTION METHOD USING THE DNA NETWORK AS A MASK

In standard manufacturing procedures of microelectronic circuits, large patterns are made and then photographically placed in reduced form on the chip. In these standard procedures a circuit is designed and used to prepare a set of final-size master masks, which are then reproduced on chips. The DNA networks can be used directly as master masks for the manufacture of microelectronic circuits, avoiding size-reduction intermediate procedures, i.e., the DNA or DNA-protein patterns can be used directly as photomasks in the step of the photolithographic procedure in which the oxidised wafer (silicon dioxide or similar) coated with a layer of a light sensitive material is exposed to ultra-violet light through the photomask (in this case, through the DNA). Also in this case, the network can be changed by deposition or exchange into a network of another material as described under II.

REFERENCES

(1) JD Watson et al. Molecular biology of the gene, Chap. 9, p. 240-281 and refs therein. The Benjamin/Cumming Publ Comp Inc. 4th Ed. (1987).
(2) MJ Mclean and RD Wells (1988) The role of sequence in the stabilization of left-handed DNA helices in vitro and in vivo. Biochim Biophys Acta, 950, 243-254.
(3) J Hurwitz, A Bresler and R Dizingen (1960) The enzymatic incorporation of ribonucleotides into polynucleotides and the effect of DNA. Biochem Biophys Res Comm 3, 15-19.
(4) W Fiers (1979) Structure and function of RNA. Bacteriophages Comp Virology 13, 69.
(5) C Brack (1981) DNA electron microscopy. CRC Critical Reviews in Biochemistry 10, 113-169.
(6) J Ferguson and RW Davis (1978) Quantitative electron microscopy of nucleic acids. In: Advanced Techniques in Electron Microscopy 2, 123-171. Ed. I. Koehler, Springer, N.Y.
(7) A Efstratiadis, AM Kafatos, AM Maxam and T Maniatis (1976) Enzymatic in vitro synthesis of globin genes. Cell 7, 279.
(8) T Maniatis, EF Fritsch and J Sambrook. Molecular Cloning, A Laboratory Manual. Cold Spring Harbor, USA. Laboratory Press, N.Y. (1982).
(9) B Weiss et al. (1968) Enzymatic breakage and joining of deoxyribonucleic acid. J Biol Chem 243, 4543.
(10) AD Johnson, BI Meyer and M Ptashne (1979) Interaction between DNA-bound repressors govern regulation by lambda phage repressors. Proc Natl Acad Sci 76, 5061.
(11) JD Watson et al. Molecular Biology of the Gene. Chap.16 & 17. The Benjamin/Cummings Publ Com Inc., 4th Ed. (1987)
(12) F Sherman, GR Fink and JB Hicks. Laboratory Course Manual for Methods in Yeast Genetics, Cold Spring Harbor Laboratories, USA (1986).
(13) DT Burke, GF Carle and MV Olson (1986) Science 236, 806-812.

Claims

1. Molecular micronetwork for electronic microcircuits characterized in that the network contains double and/or single stranded nucleic acid molecules whereby the molecular pattern of the micronetwork is formed by synthesis of specific nucleic acid molecules and/or hybridization of nucleic acid molecules and/or fixation thereof to DNA-binding proteins.

2. Micronetwork according to claim 1 characterized in that the nucleic acid comprises single and/or double stranded DNA and/or RNA.

3. Micronetwork according to claim 1 and/or claim 2 characterized in that the network contains (1) a defined orientation (start and end point), (2) single stranded and/or double stranded regions defined by position, length and sequence, (3) branching sites and (4) connection sites.

4. Micronetwork according to claims 1 to 3 characterized in that certain regions of the nucleic acid network are fixed by specific binding to a DNA binding protein which has been bound to a hydrophobic substrate.

5. Micronetwork according to claim 4 characterized in that the DNA binding protein is the λ-repressor protein.

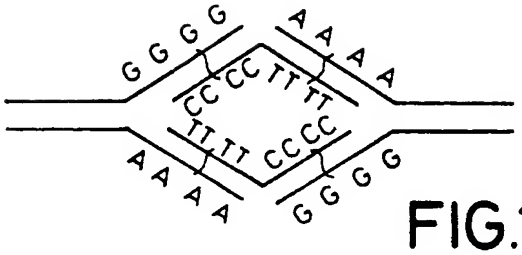
6. Micronetwork according to claim 4 characterized in that the DNA binding protein is the lac repressor protein.

7. Method for the production of a micronetwork according to claim 1 characterized in that the network is formed by DNA and RNA synthesis reactions and hybridization of the synthesized nucleic acids with preconstructed nucleic acid network components.

8. Method for the production of a conductive micronetwork for a chip characterized in that electricity conducting substances are deposited at the molecular network according to any of claims 1 to 6.

9. Method according to claim 8 comprising the following steps:
(a) Production of a molecular network fixed onto a substrate according to any of the claims 1 to 6.
(b) Shadowing under low angle with a masking substance so that the substrate stays free only along the strands of the network.
(c) A further shadowing step by metallo-organic chemical vapour deposition using electron conductive material, preferentially doped gallium arsenide or doped silicium.
(d) Selective removal of the masking substance and the original network substance so that only the conducting material forming the network is left.
(e) Deposition of a second electricity conductive substance, preferably of gallium arsenide.

10. Method for the construction of masks for the production of chips by photolithographic procedure comprising the following steps:
(a) Production of a molecular and substrate-fixed network according to claim 1.
(b) Shadowing under low angle with a masking, electron dense substance so that the substrate is free only along the strands of the network,
(c) or alternatively converting the network into an electron dense substance.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A A A A
G G G G

FIG.1

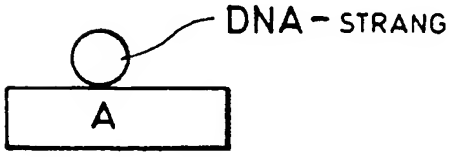
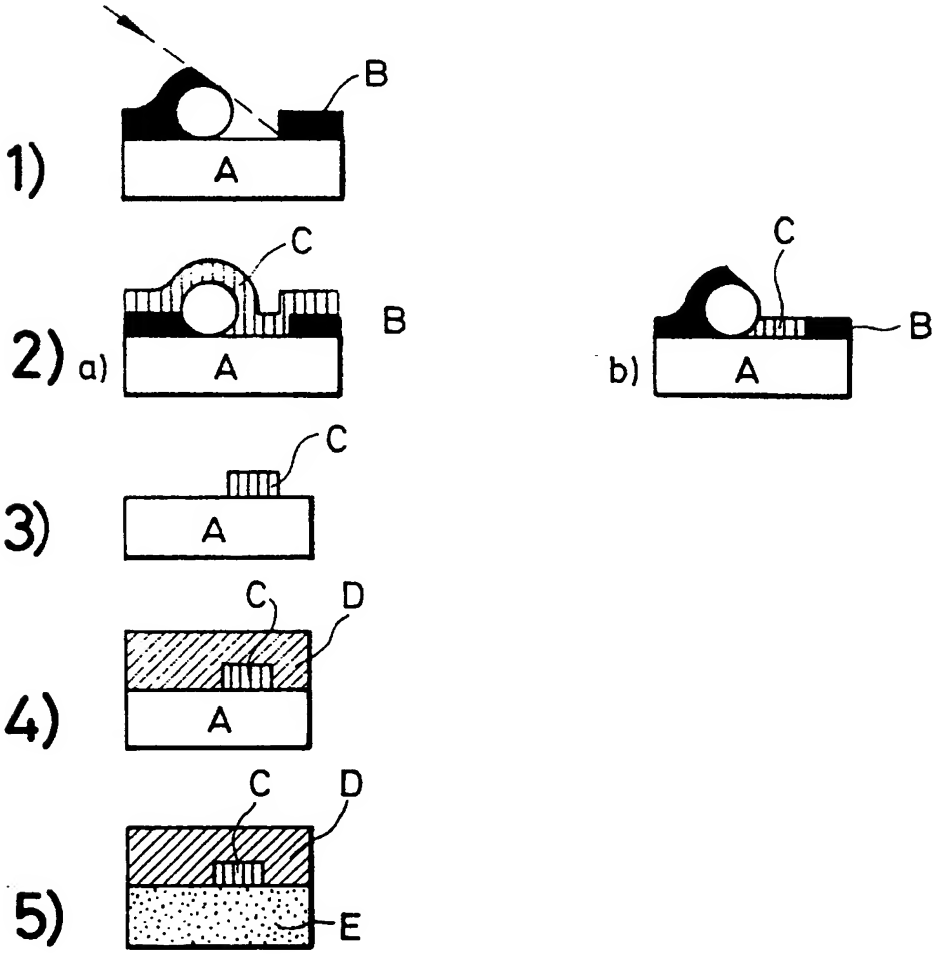

DNA - STRANG
A

FIG. 2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EUROPEAN SEARCH REPORT

Application Number

EP 90 12 3745

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X Y	F.L. CARTER 'Molecular electronic devices' 1983 , MARCEL DEKKER INC , NEW-YORK * page 213, line 1 - page 220, line 21 * ---	1-4,7 5,6,8-10	G06F15/80 H01L21/32
D,Y	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA. vol. 76, no. 10, October 1979, WASHINGTON US pages 5061 - 5065; A.D. JOHNSON: 'Interactions between DNA-bound repressors govern regulation by the L phage repressor ' * abstract * ---	5,6	
Y	US-A-4 103 064 (MCALEAR ET AL.) July 25, 1978 * column 1, line 1 - column 2, line 45 * * column 3, line 10 - column 4, line 46 * * column 7, line 34 - column 8, line 17 * ---	8-10	
E,X	DE-A-3 924 454 (HOLLENBERG) February 7, 1991 * the whole document * ---	1-10	
A	F.L. CARTER 'Molecular electronic devices' 1983 , MARCEL DEKKER , NEW YORK * page 175, line 1 - page 178, line 3; figure 3 * -----	1,2,8-10	TECHNICAL FIELDS SEARCHED (Int. Cl.5) G05F H01L G06F

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	01 AUGUST 1991	SCHENKELS P.F.

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